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90-0074448

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : C07H 19/06, 19/10, 19/24; A61K 31/70, C07D 239/47; C07D 239/54, 401/04, 403/04; C07D 405/04, 409/04, 421/04 — A1

(11) International Publication Number: WO 89/12061

(43) International Publication Date: 14 December 1989 (14.12.89)

(21) International Application Number: PCT/SE39/00322

(22) International Filing Date: 7 June 1989 (07.06.89)

(30) Priority data: 8802173-8 10 June 1988 (10.06.88) SE

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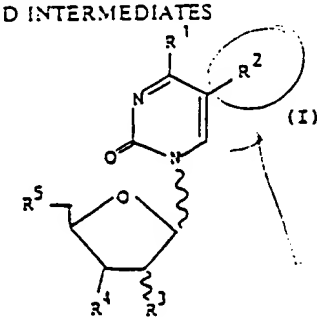
(81) Designated States: AU, DK, FI, HU, JP, KR, NO, US.

Published
With international search report.

NEW 1-RIBOFURANOSYL-5-HETEROCYCLYL OR ARYL-PYRIMIDIN-2-ONE DERIVS. USEFUL AS ANTIVIRAL AGENTS, ESP. AGAINST HIV, HEPATITIS B AND HERPES, AND NEW 1-UNSUBSTD. PRECURSORS

(54) Title: PYRIMIDINE NUCLEOSIDES AND INTERMEDIATES



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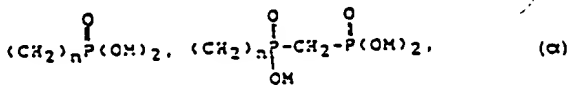

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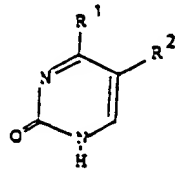

(I')

(57) Abstract

Compounds of formula (I), wherein R^1 is OH, NH_2; R^2 is a heteroaromatic or aromatic substituent as defined in claim 1; R^3 is H, OH, F, OCH_3; R^4 is H, F, OH or an ether or ester residue thereof, OCH_3, CN, C≡CH, N_3; R^5 is OH or an ether or ester residue thereof including mono-, di- and triphosphate esters; (α), wherein n is 0 or 1 and M is hydrogen or a pharmaceutically acceptable counterion such as sodium, potassium, ammonium or alkylammonium; and pharmaceutical compositions comprising said compounds can be used for therapeutic and/or prophylactic treatment of virus infections such as AIDS. Compounds of formula (I'), wherein R^1 and R^2 are as defined above, are new precursor compounds.

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Pyrimidine nucleosides and intermediates.

Field of the invention

The present invention relates to novel chemical compounds and pharmaceutically acceptable salts thereof which can be used in theraphy for therapheutic and prophylactic treatment of the acquired immuno deficiency syndrome (AIDS) and infections caused by viruses requiring reverse transcriptase for replication, such as human immuno deficiency viruses and hepatitis B viruse, and also for treatment of other virus diseases, such as those of herpes viruses, diseases which include both common infections and neoplastic diseases, i.e. cancer. The invention also relates to novel precursor compounds constituting a further aspect of the invention.

Background of the invention

The effects of viruses on bodily functions is the end result of changes occurring at the cellular and subcellular levels. The pathogenic changes at the cellular level are different for different combinations of viruses and host cells. While some viruses cause a general destruction (killing) of certain cells, other may transform cells into a neoplastic state.

Important common viral infections are herpes dermatitis (including herpes labialis), herpes keratitis, herpes genitalis, herpes zoster, herpes encephalitis, infectious mononucleosis and cytomegalovirus infections all of which are caused by viruses belonging to the herpes virus group. Other important viral diseases are influenza A and B which are caused by influenza A and B virus respectively. Another important common viral disease is viral hepatitis and especially hepatitis B virus infections are widely spread. Effective and selective antiviral agents are needed for treatment of these diseases as well as for other diseases caused by viruses.

Several different viruses of both DNA and RNA type have been shown to cause tumors in animals. The effect of cancerogenic chemicals can on animals result in activation of latent tumor viruses. It is possible that tumor viruses are involved in human tumors. The most likely human cases known today are leukemias, sarcomas, breast carcinomas, Burkitt lymphomas, nasopharyngeal carcinomas and cervical cancers where RNA tumor viruses and herpes viruses are indicated and papillomas where papilloma viruses are involved. This makes the search for selective inhibitors of tumorogenic viruses and their functions an important undertaking in the efforts to treat cancer.

In the late seventies a new disease was reported, which subsequently was referred to as Acquired Immuno Deficiency Syndrome (AIDS). It is now generally accepted that a retrovirus referred to as HIV (Human Immunodeficiency Virus), formerly known as Human T-cell Lymphotropic Virus (HTLV-III) or Lymphadenopathy Associated Virus (LAV) plays an essential role in the etiology of AIDS. Different types of HIV have been found, such as HIV-1 and HIV-2 and more are likely to be isolated.

AIDS is characterized by a profound immunodeficiency due to low numbers of a subset of lymphocyte-T-helper cells, which are one target for HIV infection. The profound immunodeficiency in AIDS patients makes these patients highly susceptible to a variety of opportunistic infections of bacterial, fungal, protozoal or viral etiology. The etiological agents among viral opportunistic infections are often found in the herpes virus group, i.e. herpes simplex virus (HSV), Varicella Zoster virus (VZV), Epstein-Barr virus (EBV) and, especially, cytomegalovirus (CHV). Other retroviruses affecting humans are HTLV-I and II and examples of retroviruses affecting animals are feline leukemia virus and equine infectious anaemia virus. Human diseases such as multiple sclerosis, psoriasis, tropical spastic paresis and Kawasaki disease have also been reported to be associated with retrovirus infections.

Hepatitis B virus infections cause severe disease such as acute hepatitis, chronic hepatitis, fulminant hepatitis in a considerable number of persons. It is estimated that there are 200 million patients with chronic hepatitis B infection in the world. A considerable number of the chronic cases progress to liver cirrosis and liver tumours. In some cases the hepatitis infections also take a rapid and severe course as in fulminant B hepatitis with about 90% mortality. At present there is no known effective treatment against hepatitis B infections. The replication of hepatitis B virus is similar to that of retroviruses and it contains the same essential viral reverse transcriptase activity.

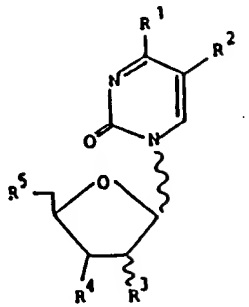
General outline of the invention

A great number of nucleoside analogues exhibit several antimetabolic activities. They do so by substituting for or competing with the naturally occuring nucleosides. Recently some nucleoside analogues have been described, which inhibit in cell culture the multiplication of human immunodeficiency virus (HIV, also called HTLV-III, LAV) the causative agent of AIDS and AIDS-related complex (ARC).

We have now found that activities for inhibition of HIV and/or herpes multiplication are exhibited by nucleoside analogues, in which the pyrimidine bases are substituted in the 5-position by a heteroaromatic, or aromatic substituent. The nucleoside analogues may be either alpha- or beta-anomers.

Disclosure of the invention

The present invention relates to new compounds of the formula I



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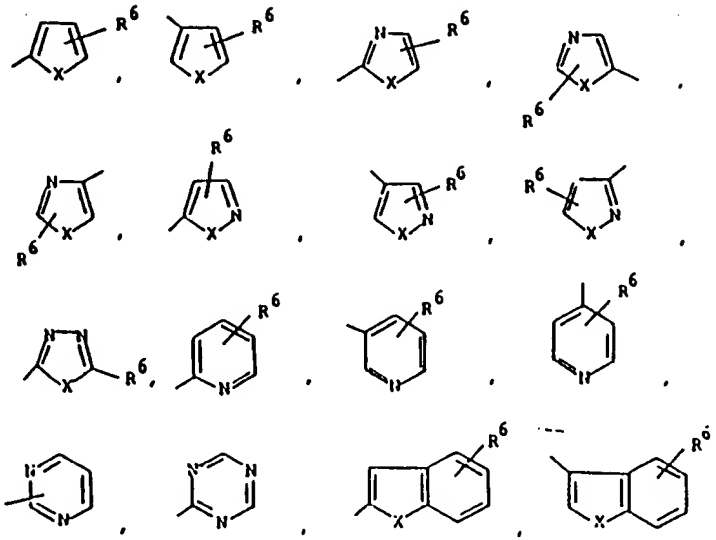
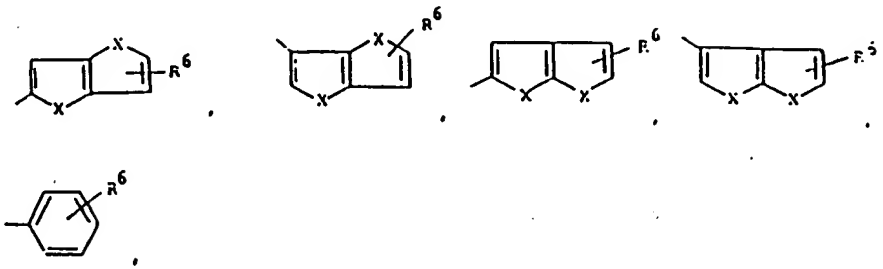
wherein the radicals R^1, R^2, R^3, R^4 and R^5 are defined as follows:

R^1: OH, NH_2;

R^2:





wherein X is O, S, N-R^7, Se;

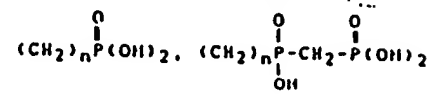
R^6 is H, straight or branched C_{1-10} alkyl, F, Cl, Br, I, X-R^7, -CH=CH-R^7, -C≡C-R^7, CO_2R^7, CH_2X-R^7;

R^7 is H, straight or branched C_{1-5} alkyl, phenyl;

R^3: H, OH, F, OCH_3;

R^4: H, F, OH or an ether or ester residue thereof, OCH_3, CN, C≡CH, N_3;

R^5: OH or an ether or ester residue thereof;



wherein n is 0 or 1 and H is hydrogen or a pharmaceutically acceptable counterion such as sodium, potassium, ammonium or alkylammonium; and pharmaceutically acceptable salts thereof. Said compounds have been found to inhibit the multiplication of human immunodeficiency virus (HIV).

The invention consequently also refers to the compounds of the formula I for use in therapy. The compounds of the formula I are useful as a therapeutic and/or prophylactic agents in the control and treatment of HIV virus infections in man. In a more general aspect, the compounds of the formula I are useful as therapeutic and/or prophylactic agents in the control and treatment of infections caused by retroviruses and hepatitis B virus in mammals and man.

All retroviruses, including HIV, require the enzyme reverse transcriptase in their natural cycle of replication.

Hepatitis B virus (HBV) is a DNA virus with a unique circular double-stranded DNA genome which is partly single-stranded. It contains a specific DNA polymerase required for viral replication. This DNA polymerase also acts as a reverse transcriptase during the replication of HBV DNA via an RNA intermediate.

The compounds of the formula I inhibit the activity of reverse transcriptase of retroviruses including HIV as well as the activity of DNA polymerase of hepatitis B virus.

Another important area of use for the compounds of the formula I is in the treatment of herpes virus infections. Among the herpes viruses may be mentioned Herpes simplex type 1 and 2, varicella (Herpes zoster), virus causing infectious mononucleosis (i.e. Epstein-Barr virus), cytomegalovirus and human herpes virus type 6. Important diseases caused by herpes viruses are herpes dermatitis (including herpes labialis), herpes genitalis, herpes keratitis, herpes encephalitis and herpes zoster.

Another possible area of use for the compounds of the present invention is in the treatment of cancer and tumors, particularly those caused by viruses. This effect may be obtained in different ways, i.e. by inhibiting the transformation of virus-infected cells to a neoplastic state, by inhibiting the spread of viruses from transformed cells to other normal cells and by arresting the growth of virus-transformed cells.

The invention furthermore provides:

A pharmaceutical composition comprising a compound of the formula I as an active ingredient and a pharmaceutically acceptable carrier, including liposomes; and

A method for therapeutic and/or prophylactic treatment of virus infections in an animal or human host in need of treatment comprising administering an effective amount of a compound of the formula I.

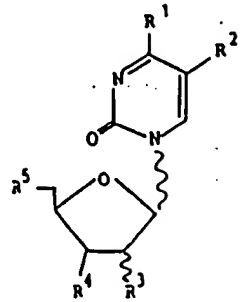
It is a preferred aspect of the invention to treat infections caused by herpes viruses or viruses requiring reverse transcriptase for replication, including human immuno deficiency viruses and hepatitis B virus.

The invention also relates to the use of a compound of the formula I for the manufacture of a medicament for therapeutic and/or prophylactic treatment of the acquired immuno deficiency syndrome and infections caused by viruses requiring reverse transcriptase for replication.

Preferably they can be used for the treatment of infections caused by HIV viruses or hepatitis B virus.

The nucleoside analogues of the invention are composed of a 5-substituted uracil or cytosine base and a sugar moiety which can for instance be ribose, 2'-deoxyribose, 2',3'-dideoxyribose, arabinose, or analogues thereof.

Preferred compounds of the formula I



I

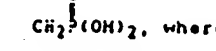
are those wherein

R^2 is 2-furyl, 2-thienyl, selenienyl, thiazolyl, 2-(1-alkyl)pyrrolyl or methoxyphenyl;

R^3 is hydrogen, hydroxy or fluoro;

R^4 is hydrogen, hydroxy, fluoro, cyano or azido; and

R^5 is hydroxy, a mono-, di- or triphosphate thereof or



wherein H is a pharmaceutically acceptable counterion.

Examples of especially preferred compounds are those of the formula I wherein:

R^1	R^2	R^3	R^4	R^5
OH	2-furyl	H	OH	OH or triphosphate
OH	2-thienyl	H	OH	OH or triphosphate
OH	2-selenienyl	H	OH	OH or triphosphate
OH	2-thiazolyl	H	OH	OH or triphosphate
OH	2-furyl	OH	OH	OH or triphosphate
OH	2-thienyl	OH	OH	OH or triphosphate
OH	2-selenienyl	OH	OH	OH or triphosphate
OH	2-thiazolyl	OH	OH	OH or triphosphate
OH	2-furyl	OH	F	OH or triphosphate
OH	2-thienyl	OH	F	OH or triphosphate
OH	2-selenienyl	OH	F	OH or triphosphate
OH	2-thiazolyl	OH	F	OH or triphosphate
OH	2-furyl	OH	N_3	OH or triphosphate
OH	2-thienyl	OH	N_3	OH or triphosphate
OH	2-selenienyl	OH	N_3	OH or triphosphate
OH	2-thiazolyl	OH	N_3	OH or triphosphate
OH	2-furyl	H	H	OH or triphosphate
OH	2-thienyl	H	H	OH or triphosphate
OH	2-selenienyl	H	H	OH or triphosphate
OH	2-thiazolyl	H	H	OH or triphosphate

OH	2-furyl	H	F	OH or triphosphate
OH	2-thienyl	H	F	OH or triphosphate
OH	2-selenienyl	H	F	OH or triphosphate
OH	2-thiazolyl	H	F	OH or triphosphate
OH	2-furyl	H	N_3	OH or triphosphate
OH	2-thienyl	H	N_3	OH or triphosphate
OH	2-selenienyl	H	N_3	OH or triphosphate
OH	2-thiazolyl	H	N_3	OH or triphosphate
OH	2-furyl	H	OH	methylphosphonate
OH	2-thienyl	H	OH	methylphosphonate
OH	2-thiazolyl	H	OH	methylphosphonate
OH	2-furyl	H	H	methylphosphonate
OH	2-thienyl	H	H	methylphosphonate
OH	2-thiazolyl	H	H	methylphosphonate
OH	2-furyl	H	F	methylphosphonate
OH	2-thienyl	H	F	methylphosphonate
OH	2-thiazolyl	H	F	methylphosphonate
OH	2-furyl	H	N_3	methylphosphonate
OH	2-thienyl	H	N_3	methylphosphonate
OH	2-thiazolyl	H	N_3	methylphosphonate
OH	2-furyl	OH	F	methylphosphonate
OH	2-thienyl	OH	F	methylphosphonate
OH	2-thiazolyl	OH	F	methylphosphonate

Esters and ethers of the nucleosides are also included in the invention. Examples of esters are mono-, di- and tri-phosphate esters, carboxylic esters, carbonate esters, carbamate esters and sulphonic esters. The acid part of the esters may have alkyl, aryl or arylalkyl chains, where the aryl functionalities are optionally substituted for example by alkoxy, amino, nitrile, alkyl or sulphonamido groups or by one or more halogen atoms. Examples of other types of derivatives of the nucleosides are alkyl or arylalkyl derivatives of the 5-hydroxyl group. The arylalkyl ether derivatives may be for example benzyl or tri-phenyl methyl and the aryl moiety may be optionally

substituted. Furthermore, it is understood that the examples of the pharmaceutically acceptable salts cited below also apply to the various esters or derivatives of the nucleosides of the invention.

In a compound of the formula I R^5 as an ether residue can be defined as OR^8, wherein R^8 is C_{1-6} alkyl, arylalkyl optionally substituted with one or more alkoxy, amino, nitrile or sulphamido groups or one or more halogen atoms.

R^4 and R^5 as an ester residue can be derived from a carboxylic acid R^9COOH, a carbonic acid $R^{10}OCOOH$, a double ester of a carbonic acid $R^{10}CO_2CH(R^{11})OCO_2H$, a sulphonic acid $R^{10}SO_2OH$, a carbamic acid $R^{10}NHCOOH$ or a phosphoric acid, wherein R^9 is hydrogen, C_{1-17} alkyl, alkoxyalkyl, arylalkyl or aryl, R^{10} is C_{1-17}, arylalkyl or aryl, R^{11} is hydrogen or C_{1-3} alkyl and said aryl and arylalkyl groups optionally can be substituted with one or more alkyl, alkoxy, amino, nitrile, sulphonamido groups or one or more halogen atoms.

Examples of pharmaceutically acceptable salts of the compounds of formula I include base salts , e.g. derived from an appropriate base, such as alkali metal (e.g. sodium, potassium, alkaline earth metal, e.g. magnesium) salts, ammonium and NX_4^+ (wherein X is C_{1-4} alkyl). Physiologically acceptable acid salts include salts of organic carboxylic acids such as acetic, lactic, gluconic, citric, tartaric, maleic, malic, pantothenic, isethionic, oxalic, lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic, p-chlorobenzenesulphonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, hydroiodic, sulfuric, phosphoric and sulfamic acids.

Physiologically acceptable counterions M of the phosphonate groups include inorganic and organic counterions. Inorganic

counterions are for example ammonium, sodium, potassium, lithium, magnesium and calcium. Organic counterions are derived from non-toxic bases, such as primary, secondary and tertiary amines, including naturally occuring amines. Examples of such amines are diethylamine , triethylamine, isopropylamine, ethanolamine, morpholine, 2-diethylaminoethanol, glucosamine, N-methylglucamine, piperazine and dicyclohexylamine.

In clinical practice the pyrimidine derivatives of the formula I will normally be administered orally, by injection or by infusion in the form of a pharmaceutical preparation comprising the active ingredient in the form of the original compound or optionally in the form of a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier which may be a solid, semi-solid or liquid diluent or an ingestible capsule. The compound may also be used without carrier material. As examples of pharmaceutical preparations may be mentioned tablets, dragées, capsules, granulates, suspensions, elixirs, syrups, solutions, liposomes etc. Usually the active substance will comprise between 0.05 and 20% for preparations intended for injection and between 10 and 90% for preparations intended for oral administration.

In the treatment of patients suffering from retrovirus, especially HIV, or hepatitis B virus infections, it will be preferred to administer the compounds by any suitable route including the oral, parenteral, rectal, nasal, topical and vaginal route. The parenteral route includes subcutaneous, intramuscular, intravenous and sublingual administration. The topical route includes buccal and sublingual administration. The dosage at which the active ingredients are administered may vary within a wide range and will depend on various factors such as the severity of the infection, the age of the patient etc., and may have to be individually adjusted. As a possible range for

the amount of the compounds of the invention or a physiologically acceptable salt thereof to be administered per day may be mentioned from about 10 mg to about 10 000 mg, preferentially 100-500 mg for intravenous administration and preferentially 100-3000 mg for oral administration.

Compounds of the formula I can cooperate synergistically or additively with a wide range of other therapeutic agents, thereby enhancing the therapeutic potential of both agents without adding the toxic effects, thus increasing the therapeutic ratio.

Therefore, a compound of formula I or a pharmaceutically acceptable derivative thereof can be used in combination therapy, wherein the two active agents are present in a ratio resulting in an optimal therapeutic ratio. This can be provided either by a synergistic effect against the viral infection and/or by a decrease in toxicity while maintaining a therapeutic effect which is additive or synergistic.

The optimal therapeutic ratio is observed when the two agents are present in a ratio of 500:1 to 1:500, preferably 100:1 to 1:100, particularly 20:1 to 1:20 and especially 10:1 to 1:10.

Said combinations may conveniently be administered together, for example, in a unitary pharmaceutical formulation, or separately for example as a combination of tablets and injections administered at the same time or at different times, in order to achieve the required therapeutic effect.

The compounds of the formula I are potentiated by interferons, other antiviral agents such as foscarnet, AZT, HIV protease inhibitors, immunomodulators, interferon inducers and growth factors.

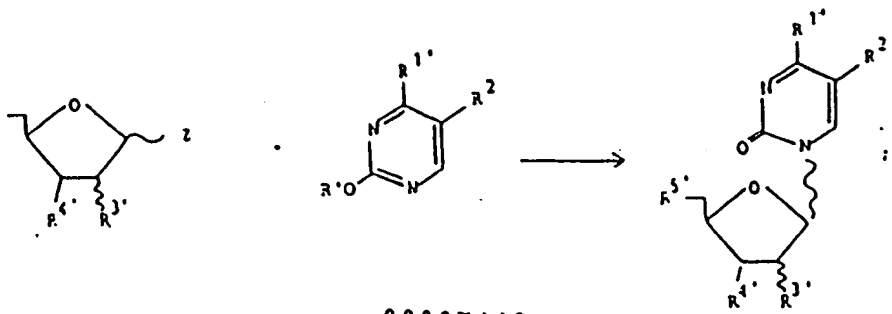
Particularly preferred types of interferon are α, β and γ and interferon inducers such as "Ampligen" (Hem Research).

Other combinations suitable for use according to the present invention include those wherein the second agent is, for example, interleukin II, suramin, foscarnet or an ester thereof, fluorothymidine, HPA 23, inhibitors of HIV protease such as pepstatin, steroids, medications such as levamisol or thymosin to increase lymphocyte numbers and/or function as appropriate, or GM-CSF and other factors regulating cell functions.

Methods of preparation

The compounds of the invention may be prepared by one of the following general methods, constituting a further aspect of the invention.

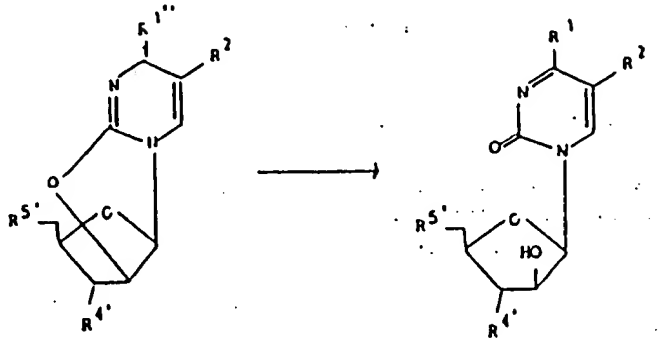
A. Condensing a glycoside as comprised in formula I where the hydroxyl groups may be optionally protected to the N-1 position of a pyrimidine derivative, according to known methods described in the literature. Such methods are described for example in "Basic Principles in Nucleic Acid Chemistry", Vol. 1 (Academic Press, 1974, Ed. P.O.P.Ts'o), in "Nucleoside Analogues, Chemistry, Biology and Medical Applications" (Pharma Press, 1979, Eds. R.T. Walker, E. De Clercq and F. Eckstein).



Examples of suitable derivatives of the reacting species are those wherein Z is Cl, Br, I, acyloxy or alkoxy; $R^{1'}$ is an alkyl or silyl protecting group, such as C_2H_5 or $(CH_3)_3Si$; $R^{1'}$ is R^1 as defined above, OC_2H_5, $(CH_3)_3SiO$, or $N(COCH_3)Si(CH_3)_2$; R^2 is as defined above; $R^{3'}$ and $R^{4'}$ is R^3 and R^4 respectively as defined above with the proviso that when R^3 or R^4 is OH said OH must be protected as O-acyl, O-benzoyl, O-benzyl or O-silyl (e.g. dimethyl, tert-butylsilyl); and $R^{5'}$ is R^5 as defined above or OR^8 wherein R^8 is as defined above or silyl (e.g. dimethyl, tert-butylsilyl). After condensation the products may be hydrolyzed or converted by conventional methods, known to those skilled in the art, into compounds of the formula I.

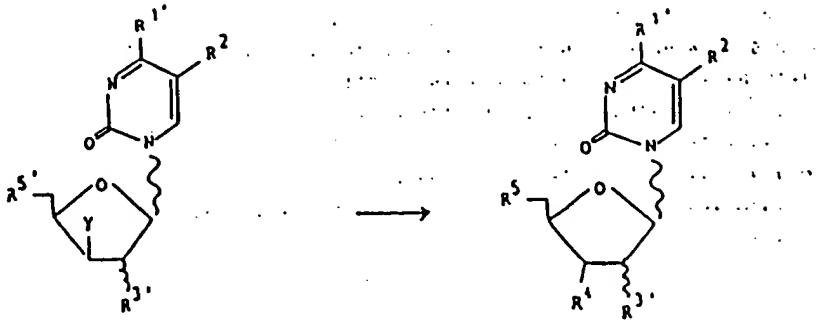
The glycosides are known or may be prepared by suitable adaptions of known methods. The syntheses of a 2,3-dideoxy-3-fluoro-erythro-pentofuranoside for example, has been described by G.W.J. Fleet and J.C. Son in Tetrahedron Letters 40 (1987) pp 3615-3618. The other 3- substituents may be introduced by methods analogous to those described above and described by N.B. Dyathina and A.V. Azhayev in Syntheses 1984 pp 961-963. The arabinosylglycosides may be prepared by similar methods.

B. The β-anomers of the arabinosyl-pyrimidine nucleoside analogues may be prepared by hydrolysis of the corresponding 2,2'-anhydro nucleoside analogues.



wherein $R^{1''}$ is O or NH and R^1, R^2, $R^{4'}$ and $R^{5'}$ are as defined above. The hydrolysis may be performed by conventional methods, described in the literature and known to those skilled in the art. It may for example be performed by treating the 2,2'-anhydronucleosides with an aqueous acid.

C. The halogeno, OCH_3, N_3, CN and C≡CH substituents in the 3'-position of the glycon moiety may be introduced by substitution of a hydroxyl group or a suitably derivatized hydroxyl group



wherein Y is OH or a functionality that will be leaving in the substitution reaction such as for example CF_3SO_3; and $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ and $R^{5'}$ are as defined above.

The following examples will further illustrate the invention:

Example 1 1-(2-Deoxy-3,5-di-O-p-toluoyl-alpha-D-ribofuranosyl)--5-(furyl)uracil (VSB 005) and

Example 2 1-(2-deoxy-3,5-di-O-p-toluoyl-beta-D-ribofuranosyl)--5-(2-furyl)uracil (VSB 006)

5-(2-Furyl)uracil (150 mg, 0.84 mmol) in hexamethyldisilazane (10 ml) was heated at reflux for 5 hours together with chlorotrimethylsilane (10 drops) and ammoniumsulfate (a few mg). The solution was filtered and evaporated in vacuo to dryness to give bis-trimethylsilylated 5-(2-furyl)uracil (240 mg) as a crude product. This crude product was dissolved in acetonitrile (15 ml, dried over molecular sieves) and added to a solution of 2-deoxy-3,5-di-O-p-toluoyl)-D-erythro-pentosyl chloride (331 mg, 0.85 mmoles; prepared according to C.C.Bhat in Synthetic Procedures in Nucleic Acid Chemistry, Vol. 1, p. 521, Interscience Publ. 1968; W.W. Zorbach and R.S. Tipson eds.) in dried acetonitrile (20 ml) and stirred over night at ambient temperature under an athmosphere of nitrogen. The solution was filtered, evaporated in vacuo and the residue was separated by chromatography on a column of silica to give pure samples of the alpha-anomer (62 mg) and of the beta-anomer (29 mg, m.p. 190-192°C). Thin layer chromatography (silica, dichloromethane-ethylacetate 5-1) R_f: alpha 0.37; beta 0.50.

Example 3 1-(2-Deoxy-3,5-di-O-p-toluoyl-alpha-D-ribofuranosyl)--5-(2-thienyl)uracil (VSA 128) and

Example 4 1-(2-deoxy-3,5-di-O-p-toluoyl-beta-D-ribofuranosyl)--5-(2-thienyl)uracil (VSA 125)

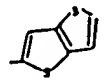
5-(2-Thienyl)uracil (0.97 g, 5 mmol) in hexamethyldisilazane (10 ml) was heated at reflux for about 2.5 hours together with chloro trimethylsilane (10 drops) and ammoniumsulfate (a few mg). The solution was filtered and evaporated in vacuo to dryness to give bis-trimethylsilylated 5-(2-thienyl)uracil, which was dissolved in 1,2-dichloroethane (25 ml, dried over molecular sieves) and added to a solution of 2-deoxy-3,5-di-O-p-toluoyl)-D-erythro-pentosyl chloride (1.55 g, 4 mmoles; prepared according to C.C. Bhat in Synthetic Procedures in Nucleic Acid Chemistry, Vol. 1, p. 521, Interscience Publ. 1968; W.W. Zorbach and R.S. Tipson eds.) in dry 1,2-dichloroethane (25 ml). Molecular sieves (2 g, 4Å) was added and the mixture was stirred at ambient temperature over night after which it was filtered. The solution was washed with an aqueous, saturated solution of sodium bicarbonate (50 ml) and water (50 ml), dried over sodium sulfate, concentrated to a volume of about 25 ml and refrigerated. The precipitate was filtered and recrystallized from 1,2-dichloroethane to give pure β-anomer (0.70 g). The remaining combined solutions were evaporated and the residue was separated on a column of silica eluted with chloroform-ethyl acetate 5-1, to give the pure alpha-anomer, VSA 128, (0,51 g, m.p. 201-3°C) and the pure beta-anomer, VSA 125, (total combined yield 0.86 g, m.p. 217-9°C). Thin layer chromatography (silica, chloroform-ethyl acetate 5-1) R_f: alpha 0.23; beta 0,30.

Analysis for $C_{29}H_{28}N_2O_7S$; calculated (found) %:
alpha: C 63.72 (63.5); H 4.80 (4.8); N 5.13 (5.0);
beta: C 63.72 (63.2); H 4.80 (4.8); N 5.13 (5.1).

Analogous to examples 1 and 2, table 1 lists some further examples which were characterized as shown in table 2.

Table 1 Examples of 1-(2-deoxy-3,5-di-O-p-toluoyl-alpha/beta-D-ribofuranosyl)-5-R^2-uracil compounds

Example	alpha/beta	R^2
1	alpha	2-furyl
2	beta	2-furyl
3	alpha	2-thienyl
4	beta	2-thienyl
5	alpha	3-furyl
6	alpha	3-thienyl
7	beta	3-thienyl
8	alpha	2-selenienyl
9	beta	2-selenienyl
10	alpha	3-selenienyl
11	beta	3-selenienyl
12	alpha	2-pyridyl
13	alpha	3-pyridyl
14	alpha	4-pyridyl
15	alpha	2-(5-methyl)thienyl
16	beta	2-(5-methyl)thienyl
17	alpha	2-(5-hexyl)thienyl
18	beta	2-(5-hexyl)thienyl
55	alpha	2-trans-tioften
56	beta	2-trans-tioften
57	alpha	2-cis-tioften
58	beta	2-cis-tioften
59	alpha	2-methoxyphenyl
60	beta	2-methoxyphenyl
61	alpha	3-methoxyphenyl



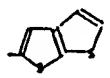


Table 2 Data for 1-(2-deoxy-3,5-di-O-P-toluoyl-alpha/beta-D-ribofuranosyl)-5-R^2-uracil compounds

Example	^{13}C NMR ($CDCl_3$)δ 1'	2'	3'	4'	5'	^1H NMR ($CDCl_3$)δ 1'	m.p. °C	Thin layer chromatography R_f
1	88.1	39.4	74.9	85.8	64.3	6.44 d		0.37 a
2	85.8	38.7	75.1	83.3	64.7	6.53 t		0.50 a
3	88.0	39.2	74.6	85.7	64.0	6.41 d	201-3	0.23 b
4	85.9	38.8	75.0	83.5	64.4	6.48 t	217-9	0.30 b
5	88.1	39.3	74.8	85.8	64.2	6.33 d (J 3.5 Hz)	179-81	0.20 b
6								
7								
8							182-4	0.22 b
9							214-6	0.33 b
10								
11								
12	88.1	39.5	74.5	85.5	64.0	6.11 d(J 3.1 Hz)		0.12 a
13	88.1	39.2	74.8	85.8	64.1	6.41 d		
14						6.44		0.10 c
15	88.0	39.2	74.8	85.7	64.2	6.41 d (J 3.3 Hz)		0.17 d
16	85.7	38.6	75.0	83.2	64.4	6.46 t		0.26 d
17	88.0	39.3	74.8	85.8	64.2	6.40 d (J 2.8 Hz)		0.22 d
18	85.7	38.5	75.0	83.2	64.4	6.49 t (J 2.0 Hz)		0.34 d

a) CH_2Cl_2-EtOAc 5-1; b) $CHCl_3$-EtOAc 5-1; c) $CHCl_3$-EtOAc 4-1;
d) $CHCl_3$-EtOAc 9-1.

Table 2 Data for 1-(2-deoxy-3,5-di-O-P-toluoyl-alpha/beta-D-ribofuranosyl)-5-R^2-uracil compounds

Example	^{13}C NMR ($CDCl_3$)δ 1'	2'	3'	4'	5'	^1H NMR ($CDCl_3$)δ 1'	m.p. °C	Thin layer chromatography R_f
55							98-101	0.57 a
56							213-217	0.70 a
57							111-115	0.41 a
58							215-218	0.54 a
59							88-90	0.23 a
60							196-198	0.55 a
61							167-169	0.28 a

Example 19 1-(2-Deoxy-alpha-D-ribofuranosyl)-5-(2-furylmethyl)uracil (VSB 007)

VSB 005 (62 mg, 0.117 mmol) was suspended in methanol (15 ml, dried over molecular sieves) and sodium methoxide in methanol (1.2 ml, 0.2 M) was added. The mixture was stirred at ambient temperature under an athmosphere of nitrogen for 24 hours, after which an ion exchanger, Dowex 50 Wx8 H^+, was added. The solution was filtered and the solvent evaporated in vacuo. The residue was purified on a column of silica eluted with ethyl acetate-ethanol 9-1, to give 1-(2-deoxy-D-ribofuranosyl)-5-(2-furyl)uracil 32 mg (93%). Thin layer chromatography (silica, ethyl acetate-ethanol 18-1) R_f: 0.42.

Example 20 1-(2-Deoxy-beta-D-ribofuranosyl)-5-(2-furylmethyl)uracil (VSB 008)

VSB 008 (28 mg, 0.055 mmol) was hydrolyzed with sodium methoxide as described for VSB 005. After completion of reaction, the dry residue of the crude product was triturated with hexane and purified on silica to give 1-(2-deoxy-β-D-ribofuranosyl)-5-(2-furyl)uracil. Thin layer chromatography (silica, ethyl acetate-ethanol 18-1) R_f: 0.47.

Example 21 1-(2-Deoxy-alpha-D-ribofuranosyl)-5-(2-thienylmethyl)uracil (VSA 134)

VSA 128 (0.35 g, 0.64 mmol) was dissolved in methanol (50 ml) and sodium methoxide in methanol (5 ml, 0.2 M) was added. The solution was stirred at ambient temperature over night, after which it was neutralized with Dowex 50Wx8 H^+. The solution was filtered, evaporated in vacuo and the residue was triturated with diethyl ether to give as a solid residue 1-(2-deoxy-α-D-ribofuranosyl)-5-(2-thienyl)uracil. Thin layer chromatography (silica, chloroform-methanol 85-15) R_f: 0.44. Analysis for

$C_{13}H_{14}N_2O_5S$, calculated (found) %: C 50.3; (50.3); H 4.55 (4.5); N 9.03 (8.8).

Example 22 1-(2-Deoxy-beta-D-ribofuranosyl)-5-(2-thienyl)uracil (VSA 133)

The title compound was prepared from VSA 125 (0.55 g, 1 mmol) in the same way as has been described for the corresponding alpha-anomer VSA 134. Thin layer chromatography for VSA 133 (silica, chloroform-methanol 85-15) R_f: 0.47.

Analogous to examples 19-22, table 3 lists some further examples which were characterized as shown in table 4.

Table 3 Examples of 1-(2-deoxy-alpha/beta-D-ribofuranosyl)-5-R^2 uracil compounds

Example	alpha/beta	R^2
19	alpha	2-furyl
20	beta	2-furyl
21	alpha	2-thienyl
22	beta	2-thienyl
23	alpha	3-furyl
24	alpha	3-thienyl
25	beta	3-thienyl
26	alpha	2-selenienyl
27	beta	2-selenienyl
28	alpha	3-selenienyl
29	alpha	2-pyridyl
30	alpha	3-pyridyl
31	alpha	4-pyridyl
32	alpha	2-(5-methyl)thienyl
33	beta	2-(5-methyl)thienyl
34	alpha	2-(5-hexyl)thienyl
35	beta	2-(5-hexyl)thienyl
62	alpha	2-trans-tioften
63	beta	2-trans-tioften
64	alpha	2-cis-tioften
65	beta	2-cis-tioften

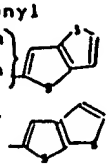


Table 4 Data for 1-(2-deoxy-alpha/beta-D-ribofuranosyl)-5-R^2-uracil compounds

Example	^{13}C NMR δ 1'	2'	3'	4'	5'	^1H NMR δ 1'	Thin layer chromatography R_f
19	91.9	42.2	72.9	89.2	63.8 a	6.35 dd (J 2.9; 1 Hz)a	0.42 c
20	89.4	42.0	72.5	87.3	63.1 a	6.44 t (J 3.3 Hz)a	0.47 c
21	92.1	42.1	73.0	89.0	63.9 a	6.24 dd (J 2.9; 1.0 Hz)b	0.44 d
22	87.8	40.6	70.3	85.1	61.2 b	6.23 t (J 3.3 Hz)b	0.47 d
23	90.2	41.7	72.8	88.3	63.6 a	6.37 dd (J 3; 1 Hz)a	0.44 e
24							
25						6.36 t (J 5 Hz) a	0.23 f
26							0.29 f
27							
28						6.29 dd (J 5; 1Hz) a	
29	91.7	42.2	72.8	89.5	63.7 a	6.33 dd (J 1.1;1.5 Hz)a	0.43 g
30	92.1	42.1	73.0	89.1	63.9 a	6.30 d (J 3.2 Hz)a	
31	90.1		70.9	86.6	62.0 b	6.13 dd (J 3.0; 0.8 Hz)b	0.15 h
32	90.0	40.2	71.0	86.3	62.1 b	6.10 d (J 3.7 Hz)b	
33	87.8	40.5	70.3	84.9	61.2 b	6.23 t (J 3.4 Hz)b	
34	90.0	40.2	71.0	86.3	62.1 b	6.10 d (J 3.1 Hz)	
35	87.8	40.5	70.3	84.9	61.2 b	6.24 t (J 3.3 Hz)	

a) CD_3OD; b) DMSO-d_6 c) EtOAc-EtOH 18-1 d) $CHCl_3$-MeOH 85-15 e) EtOAc-EtOH 9-1

f) $CHCl_3$-MeOH 7-1 g) $CHCl_3$-MeOH 5-1 h) EtOAc-MeOH 9-1

Table 4 Data for 1-(2-deoxy-alpha/beta-D-ribofuranosyl)-5-R^2-uracil compounds

Example	^{13}C NMR δ 1'	2'	3'	4'	5'	^{1}H NMR δ 1'	Thin layer chromatography R_f	m.p. °C
62								140 (dec.)
63								242 (dec.)
64								227 (dec.)
65								240 (dec.)

Table 4 Additional data for 1-(2-deoxy-alpha/beta-D-ribofuranosyl)-5-R^2-uracil compounds

Example	Elemental analysis Calculated (found) % C	H	N
25 x 1 H_2O	47.54	4.91	8.53
	(47.7)	(4.5)	8.5
28 x 0.5 H_2O	42.63	4.13	7.65
	(42.7)	(4.0)	(7.7)

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Example 36 1-(2,3-Dideoxy-α-D-ribofuranosyl)-5-(2-thienyl)uracil (VSB 533)

1-(2,3-Dideoxy-5-O-tert-butyldiphenylsilyl-α-D-ribofuranosyl-5-(2-thienyl)uracil (0.15 g) was dissolved in tetrahydrofurane, 1 M in tetrabutylammonium fluoride (3 ml) and stirred at ambient temperature for 1 hour. The solvent was evaporated and the product was purified by separation on preparative thin layer chromatography (silica, 1 mm, ethyl acetate-methanol 9-1) to give 1-(2,3-dideoxy-α-D-ribofuranosyl)-5-(2-thienyl)uracil. TLC (silica, ethyl acetate-methanol 9-1) Rf 0.54.

Example 37 1-(2,3-Dideoxy-β-D-ribofuranosyl-5-(2-thienyl)uracil (VSB 534)

Starting from 1-(2,3-dideoxy-5-O-tert-butyldiphenylsilyl-β-D ribofuranosyl-5-(2-thienyl)uracil (0.35 g) and using the same reaction conditions as described for the corresponding α-anomer in example 36, the title compound was obtained. TLC (silica, ethyl acetate-methanol, 9-1) Rf 0.59.

The starting materials for the α-and β-anomers of 1-(2,3-dideoxy-D-ribofuranosyl)-5-(2-thienyl)uracil (examples 36 and 37 respectively) were prepared by the following sequence of reactions:

a) S-γ-tert-Butyldiphenylsilyloxymethyl-γ-butyrolactone (VSB 526)

S-(+)-γ-Trityloxymethyl-γ-butyrolactone (25 g) was mixed with 80% acetic acid (aq, 400 ml) and stirred at 70-90°C for 2 hours. The solvent was evaporated in vacuo and the residue was chromatographed on a column of silica, eluted with ethyl acetate-hexane 1-2, to afford S-γ-hydroxymethyl-γ-butyrolactone (VSB 525) as

an oil (7.24 g, 80%). This product was dissolved in dry dimethyl formamide (600 ml), imidazole (10.6 g) followed by tert-butyl-diphenylchlorosilane (25 ml, 25.7 g) were added and the solution was stirred at ambient temperature for 4 hours and then at 60°C for another hour. The solvent was evaporated in vacuo, the residue was dissolved in ethyl acetate, the solution was extracted with water and brine, dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was purified by chromatography on a column of silica (ethyl acetate-hexane, 1-4) to yield S-γ-tert-butyldiphenylsilyloxymethyl-γ-butyrolactone (16.9 g, 77%) m.p. 76.5-77°C.

b) 2,3-Dideoxy-5-O-tert-butyldiphenyl-silyl-D-ribofuranose (VSB 527)

S-γ-tert-Butyldiphenylsilyloxymethyl-γ-butyrolactone (17.1 g) in dry diethyl ether (200 ml) was cooled to -78°C and stirred while diisobutylaluminum hydride in hexane (75 ml, 1.1 M) was added during 15-20 minutes. The stirring was continued for 1 hour at -78°C after which methanol (35 ml) was added and the reaction solution was allowed to come to room temperature. An aqueous sodium potassium tartrate solution (30%, 150 ml) was added with stirring. The organic phase was separated and extracted with the tartrate salt solution (4 x 75 ml). The combined aqueous portions were extracted with diethyl ether (4 x 75 ml). The combined organic solutions were dried ($MgSO_4$) and the solvent was evaporated to give 2,3-dideoxy-5-O-tert-butyldiphenylsilyl-D-ribofuranose (16.3 g) as a viscous clear oil.

c) 1-Acetyl-2,3-dideoxy-5-O-tert-butyldiphenylsilyl-D-ribofuranoside (VSB 528)

Acetic anhydride (15 ml) was added dropwise to an ice-cooled

solution of 2,3-dideoxy-5-O-tert-butyldiphenylsilyl-D-ribofuranose (7.58 g) in dry pyridine (25 ml). The stirring was continued at room temperature for 14 hours after which the reaction solution was poured onto ice and extracted with diethyl ether. The ether solution was washed with water, followed by a saturated aqueous sodium hydrogencarbonate solution, water and brine and then dried ($HgSO_4$). The solvent was evaporated to give 1-acetyl-2,3-dideoxy-5-O-tert-butyldiphenylsilyl-D-ribofuranoside as a slightly yellow oil (6.90 g, 89%).

d) 1-(2,3-Dideoxy-5-O-tert-butyldiphenylsilyl-α-D-ribofuranosyl)-5-(2-thienyl)uracil (VSB 530) and

e) 1-(2,3-Dideoxy-5-O-tert-butyldiphenylsilyl-β-D-ribofuranosyl-5-(2-thienyl)uracil (VSB 529)

5-(2-Thienyl)uracil (0.85 g) was suspended in hexamethyldisilazane (30 ml) and chlorotrimethylsilane (0.5 ml) and heated at 90°C overnight together with a small amount of ammoniumsulfate. The solvent was evaporated *in vacuo* and the residual bis-trimethylsilylated 5-(2-thienyl)uracil was dissolved in dry acetonitrile (10 ml) together with 1-acetyl-2,3-dideoxy-5-O-tert-butyldiphenylsilyl-D-ribofuranoside (1.75 g). The solution was cooled to -35°C and $SnCl_4$ (1.14 g, 0.51 ml) in dry acetonitrile (5 ml) was added dropwise. The reaction temperature was raised to -15°C and an excess of ammonia in methanol was added. The solution was allowed to reach room temperature, the solvent was evaporated *in vacuo*; the residue was extracted with ethyl acetate, filtered , the solvent was again evaporated in vacuo and the residue was subjected to chromatography on a column of silica eluted with ethyl acetate-hexane 1-9, to give the α- and β-anomers of 1-(2,3-dideoxy-5-O-tert-butyldiphenylsilyl-D-ribofuranosyl)-5-(2-thienyl)uracil.

β-anomer: 0.18 g TLC (silica, ethyl acetate-hexane, 1-1) Rf 0.42. ^{13}C NMR ($CDCl_3$)δ: 26.20 (C3'); 26.98 (CH_3); 32.7 (C2'); 65.80 (C5'); 81.68 (C4'); 86.87 (C1')); 109.78 (C5); 125.40, 126.93, 127.2, 133.2 (thienyl); 127.76, 127.88, 129.98, 135.64 (phenyl); 133.6 (C6); 149.67 (C2); 162 (C4).

α-anomer: 0.38 g, TLC (silica, ethyl acetate-hexane, 1-1) Rf 0.60. ^{13}C NMR ($CDCl_3$)δ: 26 (C3'); 27 (CH_3); 33 (C2'); 66 (C5'); 82 (C4'); 88.5 (C1'); 125, 127, 133 (thienyl); 128, 130, 136 (phenyl); 134 (C6).

Example 38 1-(2,5,6-Trideoxy-6-D-ribo-hexofuranosyl-6-phosphonic acid)-5-(2-thienyl)uracil (VSB 823).

1-(2,5,6-Trideoxy-6-dimethylphosphono-α-D-ribo-hexofuranosyl)-5-(2-thienyl)uracil (214 mg) was heated at reflux in hexamethyl-disilazane (5 ml) and acetonitrile for about 15 minutes until all material was dissolved. The solvent was evaporated, bromotrimethylsilane (0,2 ml) in acetonitrile (5 ml) was added and the solution was stirred at ambient temperature for 3 hours. Aqueous ammonia (25%, 5 ml) was added, the solvent was evaporated and the residue was dissolved in water-dimethyl sulfoxide (about 1 ml). After filtration trifluoroacetic acid (10 drops) and acetone (5 ml) was added, the precipitate was collected and washed (decanted) with acetone (3x5 ml), to yield 1-(2,5,6-trideoxy-α-D-ribo-hexofuranosyl-6-phosphonic acid)-5-(2-thienyl)-uracil. TLC (polyethylene imine, Macherey-Nagel, 0.2 M LiCl, molybdate spray-reagent) Rf 0.15.

Example 39 1-(2,5,6-Trideoxy-β-D-ribo-hexofuranosyl-6-phosphonic acid)-5-(2-thienyl)uracil (VSB 822)

Starting from 1-(2,5,6-trideoxy-6-dimethyl-phosphono-β-D-ribo-hexofuranosyl)-5-(2-thienyl)uracil (170 mg) and using the same reaction conditions as described for the corresponding α-anomer

(example 38), the title compound was obtained (40 mg). TLC (polyethylene imine, Macherey-Nagel, 0.2 M LiCl, molybdate spray reagent) Rf 0.15. ^{13}C NMR (DMSO-d6) δ : 22.70, 25.45 (C5'); 26.96 (C6'); 39.86 (C2'); 72.06 (C3'); 85.75 (C1'); 88.64, 88.98 (C4'); 108.10 (C5); 122.99, 126, 126.83, 134.55 (thienyl); 138 (C6); 149.82 (C2); 161.62 (C4).

The starting materials for the α- and β-anomers of 1-(2,5,6-trideoxy-D-ribo-hexofuranosyl-6-phosphonic acid)-5-(2-thienyl)-uracil (examples 38 and 39 respectively) were prepared by the following reaction sequence (a-h).

a) Methyl-2-deoxy-3-O-p-toluoyl-5-O-tert-butyldiphenylsilyl-D-ribofuranoside

Imidazole (18.9g) and tert-butyldiphenyl-chlorosilane (37.7 g) were added to methyl-2-deoxyribofuranoside (20.3 g) dissolved in dimethylformamid (150 ml) and the solution was stirred at ambient temperature over night. Thin layer chromatography (TLC, silica, ethyl acetate-hexane 1-4) shows the reaction product methyl-2-deoxy-5-O-tert-butyldiphenylsilyl-D-ribofuranoside with Rf 0.2. The solvent was evaporated in vacuo, the residue was dissolved in diethyl ether washed with water (4 x 50 ml), dried ($HgSO_4$) and the solvent was evaporated to give a residue (47.1g). The residue was dissolved in pyridine (200 ml), p-toluoylchloride (21.18 g) was added and the solution was stirred at ambient termperature for about 1 hour after which the solvent was evaporated in vacuo, the residue was taken up in diethyl ether and washed with water. The solution was dried ($HgSO_4$) and the solvent was evaporated in vacuo to give the title compound (50 g). TLC (silica, etyl acetate-hexane 1-4) Rf 0.5. ^{13}C NMR ($CDCl_3$) δ : 21.77 (CH_3, p-tol.); 26.73, 26.90 (CH_3, tert-but.); 39.41 (C2); 55.41 (OCH_3); 85.02 (C5); 75.85 (C3); 84.29 (C4); 105.77 (C1); 127.78, 128.34, 129.17, 129.60, 129.77, 134.96, 135.73 (C, phenyl).

b) Methyl-2-deoxy-3-O-p-toluoyl-D-ribofuranoside (VSB 818)

Methyl-2-deoxy-3-O-p-toluoyl-5-O-tert-butyldiphenylsilyl-D-ribofuranoside (50 g) was dissolved in a 1M solution of tetrabutyl-ammonium fluoride in tetrahydrofurane (100 ml). Dry sodium hydrogencarbonate (1 eq, 137 mmol) was added and the mixture was stirred at ambient temperature over night, after which the solvent was evaporated, the residue was washed with water and purified by chromatography on a silica column, eluted with ethylacetate-hexane (1-4), followed by ethyl acetate, to give the title compound (16.65 g). TLC (silica, ethyl acetate-hexane), 1-1) Rf 0.1. ^{13}C NMR ($CDCl_3$) δ : 21.80 (CH_3, p-tol.); 40.14 (C2); 55.68 (OCH_3); 64.10 (C5); 75.97 (C3); 86.35 (C4); 105.84 (C1); 129.24, 129.70, 129.80, 129.93 (C, phenyl).

c) Diphenyl (1-methyl-2,5,6-trideoxy-3-O-p-toluoyl-D-ribo-hex-5-enofuranos-6-yl)-phosphonate (VSB 818).

Pyridinium trifluoroacetate (1.89 g) (prepared from equimolar amounts of pyridine and trifluoroacetic acid in diethyl ether) and some molecular sieves (4 Å) were added to a solution of methyl-2-deoxy-3-O-p-toluoylfuranoside (5.26 g) in dimethylsulfoxide (40 ml). The solution was stirred at ambient temperature for about 30 minutes after which dicyclohexylcarbodiimide (12.2 g) was added and the stirring was continued at 60°C for 3 hours. TLC (silica, ethyl acetate-hexane, 1-4) shows a positive reaction with dinitrophenyl hydrazin-sulfuric acid spray at Rf 0.1. Methanol (20 ml) was added and stirring was continued at 60°C for another hour, after which methanol was evaporated in vacuo, the solution was filtered, diphenyl((triphenylphosphoranylidene)methyl)phosphonate (9 g; G.H. Jones, E.K.Hamamura, J. Hoffat, Tetrahedron Lett. (1968), 5371; J.A. Montgomery, A.G. Laseter, K.Hewson, J. Heterocyclic Chem. 11 (1974) 211) was

added and the solution was stirred at 70°C for 3 hours. After cooling, diethyl ether (200 ml) was added, the solution was washed with water (4 x 100 ml) and the ether solution was evaporated to dryness. The residue was purified by chromatography on a column of silica (500 g) eluted with ethyl acetate-hexane 1-4, yielding 4.4 g of diphenyl(1-methyl-2,5,6-trideoxy-3-O-p-toluoyl-D-ribo-hex-5-enofuranos-6-yl)phosphonate. ^{13}C NMR ($CDCl_3$) δ: 21.70 (CH_3, p-tol); 37.85 (C2); 56.00 (OCH_3); 77.45 (C3); 83.78, 84.24 (C4); 106.52 (C1); 115.33, 119.12 (C5); 152.40, 152.52 (C6); 165.97 (CO).

d) Diphenyl(1-methyl-2,5,6-trideoxy-3-O-p-toluoyl-D-ribo-hexofuranos-6-yl)phosphonate (VSB 819).

Diphenyl(1-methyl-2,5,6-trideoxy-3-O-p-toluoyl-D-ribo-hex-5-enofuranos-6-yl)phosphonate (4.46 g) in dry tetrahydrofurane was hydrogenated at 1 bar for 30 minutes using Pd/C (5%) as a catalyst. The reaction mixture was filtered through a celite pad, the solvent was evaporated and the residue was purified by chromatography, on silica to give the title compound (3.72 g). ^{13}C NMR ($CDCl_3$) δ: 21.53 (CH_3, p-tol); 21.21, 24.06 (C5); 27.68 (C6); 38.95(C2); 55.27 (OCH_3); 77.52 (C3); 83.68, 84.04 (C4); 105.50 (C1); 166.02 (CO).

a) 1-(2,5,6)-Trideoxy-3-O-p-toluoyl-6-diphenylphosphono-α-D-ribo-hexofuranosyl)-5-(2-thienyl)uracil (VSB 826) and

f) 1-(2,5,6-Trideoxy-3-O-p-toluoyl-6-diphenylphosphono-β-D-ribo-hexofuranosyl)-5-(2-thienyl)uracil (VSB 820)

5-(2-Thienyl)uracil (0.5 g) in dry acetonitrile (15 ml), hexamethyl disilazane (5 ml) and chlorotrimethyl silane (0.5 ml) was heated at reflux for about 30 minutes after which the solvents were evaporated to give 2,4-bis-trimethyl silylated 5-(2-thienyl)uracil. Dry acetonitrile was added, followed by

diphenyl(1-methyl-2,5,6-trideoxy-3-O-p-toluoyl-D-ribo-hexofuranos-6-yl)phosphonate (VSB 819, 1.65 g) in dry acetonitrile (10 ml) and finally tert-butyl-dimethylsilyltriflate (0.6 ml) under vigorous stirring, and the solution was stirred at ambient temperature for about 1.5 hours, after which concentrated aqueous ammonia (4 ml) was added. The solvent was evaporated in vacuo and the residue was purified by chromatography in a column of silica (100 g) eluted with ethyl acetate-hexane, 1-1, to give the α-anomer (0.58 g) and the β-anomer (0.40 g) of 1-(2,5,6-trideoxy-3-O-p-toluoyl-6-diphenyl-phosphono-D-ribo-hexofuranosyl)-5-(2-thienyl)uracil. TLC (silica, ethyl acetate-hexane, 1-1) Rf: α 0.15; β 0.20. ^{13}C NMR ($CDCl_3$)δ, α-anomer: 20.12 (CH_3, p-tol.); 19.68, 22.53 (C5'); 25.40, 25.47 (C6'); 36.81 (C2'); 76.50 (C3'); 85.84, 86.16 (C4'); 86.35 (C1'); 108.22 (C5); 122.89, 124.23, 125.49 (thienyl); 134.03 (C6). β-anomer: 21.80 (CH_3, p-tol.); 21.21, 24.08 (C5'); 27.08 (C6'); 37.27 (C2'); 76.48 (C3'); 84.12, 84.48 (C4'); 85.70 (C1'); 110.75 (C5); 124.76, 125.62, 127.17 (thienyl); 133.86 (C6).

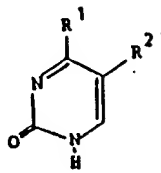
g) 1-(2,5,6)-Trideoxy-6-dimethylphosphono-α-D-ribo-hexofuranosyl)-5-(2-thienyl)uracil (VSB 825)

1-(2,5,6-Trideoxy-3-O-p-toluoyl-6-diphenylphosphono-α-D-ribo-hexofuranosyl-5-(2-thienyl)uracil (444 mg) was dissolved in 0.5 M sodium methoxide in methanol (20 ml) and stirred at ambient temperature for 3 hours. The solution was neutralized with Dowex 50W x 8 (pyridinium$^+$), filtered and the solvent was evaporated. Silica and diethyl ether-hexane was added, the solvent was decanted and the residue was again triturated with ether-hexane (4x). Finally the silica was eluted with methanol-tetrahydrofuran 1-1 and the solvent was evaporated in vacuo to give the title compound (234 mg). ^{13}C NMR (CD_3OD)δ: 18.95, 21.80 (C5'); 25.98, 26.08 (C6'); 39.75 (C2'); 52.49 (2 $POCH_3$); 73.32 (C3'); 86.28 (C1'); 88.25, 88.57 (C4'); 109.29 (C5); 123.79; 125.10, 126.59, 133.88 (thienyl); 136.59 (C6); 149.92 (C2); 161.91 (C4).

h) 1-(2,5,6)-Trideoxy-6-dimethylphosphono-ß-D-ribo-hexofuranosyl)-5-(2-thienyl)uracil (VSB 824)

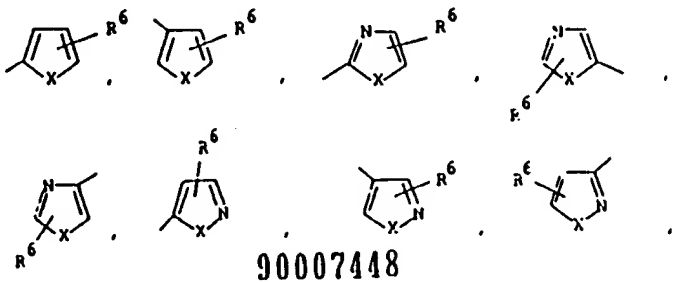
Starting from 1-(2,5,6-trideoxy-3-O-p-toluoyl-6-diphenylphosphono-β-D-ribo-hexofuranosyl)-5-(2-thienyl)uracil (326 mg) and using essentially the same reaction conditions as described for the α-anomer, the title compound was obtained. In the work-up procedure for the β-anomer no silica was included; instead the crude product was dissolved in diethyl ether and by addition of hexane the product precipitated (190 mg). ^{13}C NMR ($CDCl_3$-DMSO-d6)δ: 18.90, 21.75 (C5'); 25.98, 26.08 (C6'); 39.43 (C2'); 52.08 (2 $POCH_3$); 73.05 (C3'); 85.38, 85.45, 85.80 (C1', C4'); 109.78 (C5); 123.86, 125.13, 126.52, 133.13 (thienyl); 134.57 (C6); 149.38 (C2); 162 (C4).

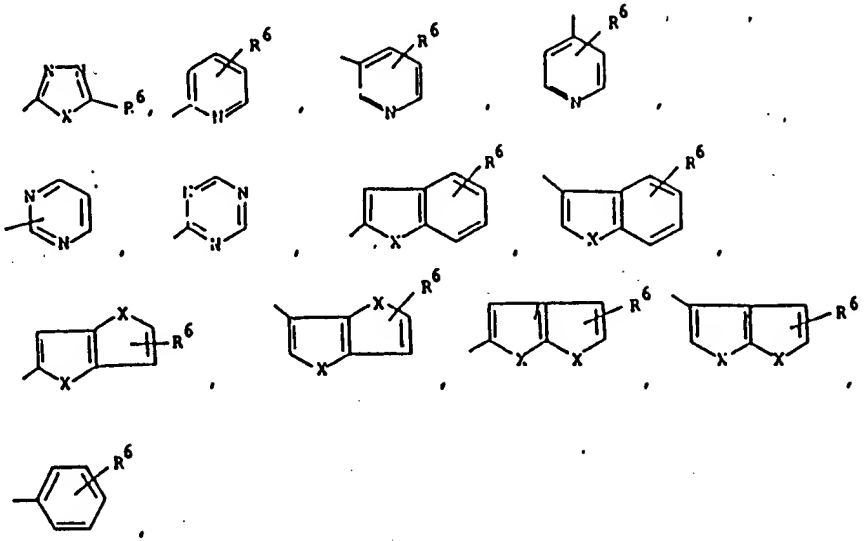
The precursor 5-substituted pyrimidine compounds of the formula I',



I'

wherein the radicals R^1 and R^2 are defined as follows:
R^1: OH, NH_2;
R^2:





wherein X is O, S, N-R^7, Se;
R^6 is H, straight or branched C_{1-10} alkyl, F, Cl, Br, I, X-R^7, -CH=CH-R^7, -C≡C-R^7, CO_2R^7, CH_2X-R^7;
R^7 is H, straight or branched C_{1-5} alkyl, phenyl;
constitute a further aspect of the invention.

The compounds of the formula I' may be prepared by the following general method:

The 2,4-dialkoxy-5-halopyrimidine compound may be reacted with the boronic acid or trialkylstannyl derivative of the heterocycle; alternatively the 2,4-dialkoxy-5-boronic acid pyrimidine or 2,4-dialkoxy-5-trialkylstannyl pyrimidine may be reacted with the halogen derivative of the heterocycle. In all cases the reaction is catalyzed by a palladium complex and performed in an organic solvent such as for example tetrahydrofuran or 1,2-dimethoxyethane at a temperature from

-20 to 100°C or at reflux for a period of 5 minutes to 2 days. After completion of the condensation reaction and work-up of the reaction mixture the 2,4-dialkoxy groupe of the pyrimidine compound are hydrolyzed by acidic hydrolysis by known methods.

The 5-substituted uracil base or the 5-substituted uridine analogue may be converted to a 5-substituted cytosine base or cytidine analogue by conventional methods, the principles of which have been described (or example by W.L. Sung (J. Chem. Soc. Chem. Commun. 1981, p. 1089 and J. Organic Chemistry 1982, volyme 47, pages 3623-3628) and by P. Herdewijn et al. (J. Medicinal Chemistry 1985, volyme 28, pages 550-555).

The following examples will further illustrate the precursor compounds of the invention.

Example 40 5-(5'-Chloro-2'-thienyl)uracil

A 250 ml flask was charged with 3.41 g (0.010 mole) of 2,4-di-tert butoxy-5-(5'-chloro-2'-thienyl)pyrimidine, 60 ml of methanol and 60 ml of 4M hydrochloric acid and the reaction mixture was stirred at room temperature for 30 min. The precipitated crystals were collected by filtration, washed with methanol and dried giving an almost quantitative yield of the title compound, mp over 300°C.
Anal. Found C 42.1, H 2.20, N 12.25, S 14.2.
Calc. for $C_8H_5ClN_2O_2S$ (228.8): C 42.02, H 2.20, N 12.25, S 14.02.

The starting material, 2,4-di-tert.butoxy-5-(5'chloro-2'-thienyl)pyrimidine, was prepared as follows:

A 100 ml flask equipped with condenser, magnetic stirrer and

nitrogen inlet was charged with 1.65 g (0.010 mol) of 2-bromo-5-chlorothiophene, 0.3 mmol of tetrakis(triphenylphosphine)-palladium(0) and 50 ml 1,2-dimethoxyethane. After stirring for 10 min, 2.95 g (0.011 mole) of 2,4-di-tert. butoxy-5-pyrimidineboronic acid was added immediately followed by 20 ml of 1 M sodium carbonate solution. The reaction mixture was refluxed for 4 hours with vigorous stirring under nitrogen. After cooling to room temperature the traces of the catalyst were filtered off, the organic solvent was evaporated under reduced pressure and the residue was diluted with water and extracted with three portions of ether. The combined etheral phases were washed with water, saturated sodium chloride solution and dried over magnesium sulphate. The solvent was evaporated and the residue purified by flash-chromatography on silica gel giving 2.6 g (76%) of 2,4-ditert. butoxy-5-(5'-chloro-2'-thienyl)pyrimidine mp 82.0-83.5°C.
Anal. Found C 55.4, H 5.24, N 8.16, S 9.52.
Calc. for $C_{16}H_{21}ClN_2O_2S$ (340.9): C 56.37, H 6.21, N 8.22, S 9.41

Example 41 5-(3'-furyl)uracil

A 100 ml flask was charged with 1.45 g (5.0 mmole) of 2,4-di-tert butoxy-5-(3'-furyl)pyrimidine dissolved in 25 ml of methanol and 25 ml of 5 M hydrochloric acid and the mixture was stirred at room temperature for 30 min. The precipitated crystals were collected by filtration, washed with methanol and dried giving the title compound in almost quantitative yield, melting with decomposition above 250°C.
Anal. C 54.1, H 3.34, N 15.5, O 27.2.
Calc. for $C_8H_6N_2O_3$ (178.1): C 53.9, H 3.39, N 15.7, O 26.8

The starting material 2,4-di-tert.butoxy-5-(3'-furyl)pyrimidine was prepared as follows

A 250 ml flask equipped with condenser, magnetic stirrer and nitrogen inlet was charged with 7.3 g (0.024 mole) of 5-bromo-2,4-di-tert-butoxypyrimidine, 0.75 mmol of tetrakis(triphenylphosphine)palladium (0) and 60 ml of 1,2-dimethoxyethane. After stirring for 10 min 3.0 g (0.027 mole) of 3-furanboronic acid was added, immediately followed by 60 ml of 1M sodium carbonate solution. The reaction mixture was refluxed for 4 hours with vigorous stirring under nitrogen. After cooling to room temperature, the traces of catalyst were filtered off, the organic solvent was evaporated under reduced pressure and the residue diluted with water and extracted with three 50 ml portions of ether. The combined etheral phases were washed with water, saturated sodium chloride solution and dried over magnesium sulphate. The ether was evaporated and the residue was purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent, yielding 4.1 g (59%) of the title compound as an oil.

Anal. Found C 66.5, H 7.68, N 9.64, O 17.0.

Calc. for $C_{16}H_{22}N_2O_3$ (290.4) C66.2, H 7.64, N 9.65, O 16.5.

Example 42 5-[2'-(N-methyl)pyrrolyl]uracil

3.0 g (9.9 mmole) of 2,4-di-tert.butoxy-5-[2'-(N-methyl)-pyrrolyl]-pyrimidine was stirred with 40 ml of methanol and 40 ml of 5 N hydrochloric acid for 30 min. The precipitated crystals were collected by filtration, washed with methanol and water and dried, yielding 1.5 g (79%) of the title compound melting with decomposition over 250°C.

Anal. Found C 56.0, H 4.70, N 22.00.

Calc. for $C_9H_9N_3O_2$ (191.2): C 56.5, H 4.47, N 22.0.

The starting material 2,4-di-tert.butoxy-5-[2'-(N-methyl)-pyrrolyl]pyrimidine was prepared as follows:

A 250 ml flask equipped with condenser, magnetic stirrer and nitrogen inlet was charged with 9.0 g (29.7 mmole) 2,4-di-tert-butoxy-5-bromopyrimidine, 1.05 g (1.50 mmole) of $PdCl_2(P(C_6H_5)_3)_2$ and 8.0 g (32.7 mmole) of N-methyl-2-trimethylstannylpyrrole in 80 ml of anhydrous tetrahydrofuran and refluxed for 20 hours. After cooling the reaction mixture, it was diluted with 200 ml of ether and washed twice with 50 ml of water. After drying with magnesium sulphate and evaporating the solvent, the compound was purified by chromatography using "silicagel 60" and a mixture of pentane-ether (9:1) as eluent, yielding 3.5 g (39%) of the title compound, mp 113-114°C.

Anal. Found C 67.0, H 8.37, N 13.7,

Calc. for $C_{17}H_{25}N_3O_2$ (303.4) C 67.3, H 8.30, N 13.8.

Analogous to example 40, table 5 gives some further examples of preparations from 2,4-di-tert.-butoxy-5-pyrimidine boronic acid and a bromo substituted heterocyclic compound. Their characteristics are given in table 6.

Table 5 Examples of 5-R^2-uracil compounds

Example	R^2	Intermediate 2,4-di-tert-butoxy-5-(R^2) pyrimidine yield%	mp °C	5-R^2-uracil yield
40	2-(5-chloro)thienyl	76	82-83.5	86
43	2-(5-methyl)thienyl	50	65-68	93
44	2-(5-hexyl)thienyl	52	oil	90
45	2-furyl	49	87-88	100
46	2-thiazolyl	49	102-103	100
47	5-thiazolyl	62	68-69	100
48	2-pyridyl	60	128-129	100
49	3-pyridyl	69	88-89	100
50	4-pyridyl	70	92-93	100
51	2-methoxyphenyl	35	90-91.5	90
52	3-methoxyphenyl	65	93-94	90
53	4-methoxyphenyl	41	92-94	90
54	2,5-dimethoxyphenyl	47	91-93	100
66	2-trans-tioften	57	108-110	
67	2-cis-tioften	60	108-110	
68	3-trans-tioften	55	105-107	
69	3-cis-tioften	27	88-90	

Table 6 ^{1}H NMR chemical shifts (ppm, in DMSO-d_6) for 5-substituted uracil compounds

Example	NH	NH	H6	H2'	H3'	H4'	H5'	H6'	CH_3	OCH_3	OCH_3	CH_2
40		11.5	8.07		7.03	7.33	-	-				
43		9.3	7.83		7.22	6.71	-	-	2.51			2.73 a
44		11.39	11.20	7.83	-	7.24	6.73	-	-			
45		11.40	11.20	7.71	-	6.83	6.57	7.62				
46		11.85	11.78	8.55	-	-	7.92	7.71	-			
47		11.56	11.61	8.22	9.11	-	8.39	-	-			
48		11.90	11.74	8.49	-	8.67	8.20	7.58	8.33			
49		11.69	11.58	8.13	9.12	-	8.70	7.98	7.76			
50		12.00	11.66	8.43	8.77	8.37	-	8.37	8.77			
51		11.17	10.97	7.38		7.03	7.30	6.93	7.20		3.73	
52		11.20		7.65	7.13	-	6.86	7.26	7.13			
53		11.19	11.02	7.53	7.48	6.94	-	6.90	4.75		3.76	
54		11.17	10.95	7.39	-	6.95	6.85	-	6.85		3.70	3.67

a) Additional bands at δ 1.64; 1.32; 0.88 with the relative intensities 2:6:3

Biological tests

Test I Effect of compounds of the formula I on HIV in H9 cells

Materials and methods: HIV infection of H9 cells

H9 cells, 10^5 cells per well on a 24 well plate, suspended in 2 ml RPMI-medium containing 10% fetal calf serum, 100 µg/ml pencillin, 10 µg/ml streptomycin sulfate and 2 µg/ml polybrene are exposed to HIV (HTLV-III_B) and different concentrations of the test compounds. The plates are incubated at 37°C in 5% CO_2 for 6-7 days. The contents in each well is then homogenized with a pipette and transferred to a centrifuge tube. After centrifugation for 10 min at 1500 rpm the supernatant is removed and the cell pellet is analyzed by fixing in methanol on glass plates. Human HIV positive serum diluted 1:80 or 1:160 is added and incubated for 30 min at 37°C. The plate is then washed with phosphate-buffered saline (PBS) containing Ca^{2+} and Mg^{2+}. Sheep antihuman conjugate (FITC) is added and after a new incubation the plate is again washed with PBS. Contrast staining is done with Evans blue and after drying the frequency of HIV antigen containing cells is determined in a microscope. The test result is shown in Table 7.

Table 7 Concentration (µM) for 50% inhibition (IC_{50}) of human immuno deficiency virus multiplication in cell culture

1-(2'-deoxy-α/β-D-ribofuranosyl)-5-R^2-uracil

α/β	R^2	Code	IC_{50} µM
α	2-thienyl	VSA 134	0.05-10
α	2-selenienyl	VSA 188	2-20
α	3-selenienyl	VSA 998	3-100
α	2-furyl	VSB 007	<10
α	2-(5-methylthienyl)	VSB 515	10->10
β	3-selenienyl	VSA 992	5->10
β	2-thienyl	VSA 189	10->10
β	2-furyl	VSB 008	10->10

Table 7 shows that the tested compounds are active inhibitors of HIV virus multiplication.

Test II Cellular toxicity

H9 cells, $2x10^7$ cells per plate, are incubated in RPMI-1640 medium containing 10% fetal calf serum, 70 mg/l penicillin, 100 mg/l streptomycin and 10 mM hepes, in absence or presence of test compounds. The number of cells per plate is determined after 48 h. Cells incubated in the absence of test compounds then underwent two cell division cycles.

F5000 cells, which are human embryo cells, $1x10^5$ cells per plate, are incubated in Eagle's minimal essential medium, supplemented with Earle's salts, non-essential amino acids, 10% fetal calf serum, 10 mM hepes, 70 mg/l penicillin and 100 mg/l streptomycin, in absence or presence of test compounds. The number of cells per plate is determined after 48 h. Cells incubated in the absence of test compounds underwent one cell division cycle. The results are given as % inhibition of cell multiplication when the concentration of the compound is 100 µM or 250 µM. The test results are given in table 8.

Table 8 Cellular toxicity on H9 and F5000 cells

1-(2'-deoxy-α/β-D-ribofuranosyl)-5-R^2-uracil

α/β	R^2	Code	% inhibition (concentration μM) H9	F 5000
α	2-thienyl	VSA 134	35(250)	0-35(100)
α	2-selenienyl	VSA 188	40(200)	15(200)
α	3-selenienyl	VSA 996	65(200)	30(200)
α	2-furyl	VSB 007		
α	2-(5-methyl)thienyl	VSB 515		
β	3-selenienyl	VSA 992	40(200)	0(200)
β	2-thienyl	VSA 189	35(200)	10(100)
β	2-furyl	VSB 008		0(200)

Table 8 shows that the concentrations at which the compounds exhibit toxicities exceed the concentrations needed for 50% inhibition of HIV multiplication as given in table 7.

Test III Inhibition of reverse transcriptases and DNA polymerases by triphosphates of compounds of the invention

The 5'-triphosphates were synthesized essentially as described (Yoshikawa, M, Kato T, Takenishi T, Bull. Chem. Soc. (Japan), 42,3505-3508, 1969; Ludwig, J., Acta Biochim. Biophys. Acad. Sci. Hung. 16, 131-133, 1981; Ruth, J.L., Cheng, Y.C., Mol. Pharmacol. 20, 415 1981.) The HIV-RT was obtained as described by Hansen et al (Hansen J, Schulze T and Moelling K, J. Biol. Chem. 262, 12393-12396, 1987) from cultures of Escherichia coli expressing the cloned HIV-pol gene. The HBV-DNAP was prepared from virus obtained from human serum, essentially as described by Nordenfelt et al (1987) (Nordenfelt E, Löfgren B, Chattopadhyaya J., Oberg B, J. Med. Virol. 22, 231-236, 1987). The HSV-2 DNAP and cellular DNAPα preparation and reaction conditions have been described by Larsson et al (Larsson A, Sundqvist A, Parnerud A-M, 1986, Mol. Pharmacol. 29, 614-621). In reactions using HIV-RT, the enzyme was incubated with

the template $(rA)_n(dT)_{12-18}$ and different concentrations of inhibitor and substrate (dTTP) as described by Vrang et al 1987, (Vrang L., Bazin H., Remaud G., Chattopadhyaya J. and Oberg B., Antiviral Res. 7, 139-145, 1987). The hepatitis B virus enzyme activity was determined with a virus preparation solubilized by non-idet P40, and endogenous nucleic acid as template, as described by Nordenfelt et al (vide supra)

Table 9 Concentration (μM) for 50% inhibition (IC_{50}) of enzymes by triphosphates of some compounds of the invention

Compound	HIV RT[1]	HBV DNAP[2]	HSV-2 DNAP[3]	DNAPα[4]
1-(2-Deoxy-beta-D-ribofuranosyl)-5-(2-thienyl)uracil-5'-triphosphate	0.015	0.11	0.06	1.6
1-(2-Deoxy-alpha-D-ribofuranosyl)-5-(2-thienyl)uracil-5'-triphosphate	2.0	18.0	11.0	80.0

1) Human immuno deficiency virus reverse transcriptase
2) Hepatit B virus DNA polymerase
3) Herpes simplex virus type 2 DNA polymerase
4) DNA polymerase alpha.

6. A compound according to any of claims 1-5, wherein R^4 and R^5 are both hydroxy.

7. A compound according to any of claims 1-5 wherein R^3 and R^4 are both hydrogen.

8. A compound according to any of claims 1-5 wherein R^3 is hydrogen and R^4 is fluoro, azido, cyano or methoxy.

9. A compound according to any of claims 1-5 wherein R^3 is hydroxy and R^4 is fluoro, azido, cyano or methoxy.

10. A compound acording to any of claims 1-5, wherein R^5 is

$-(CH_2)_n\overset{O}{\overset{\|}{P}}(OH)_2$, $-O-\overset{O}{\overset{\|}{P}}(OH)_2$ or $-O-\overset{O}{\overset{\|}{P}}(OH)-\left(O-\overset{O}{\overset{\|}{P}}(OH)\right)_n O-\overset{O}{\overset{\|}{P}}-(OH)_2$,

wherein n = 0 or 1

11. A compound according to any of claims 1-5, wherein R^5 as an ether residue is defined as OR^6, wherein R^6 is C_{1-6} alkyl, arylalkyl optionally substituted with one or more alkoxy, amino, nitrile or sulphamido groups or one or more halogen atoms.

12. A compound according to any of claims 1-5, wherein R^4 and/or R^5 as an ester residue is derived from a carboxylic acid R^9COOH, a carbonic acid $R^{10}OCOOH$, a double ester of a carbonic acid $R^{10}CO_2CH(R^{11})OCO_2H$, a sulphonic acid $R^{10}SO_2OH$, a carbamic acid $R^{10}NHCOOH$ or a phosphoric acid, wherein R^9 is hydrogen, C_{1-17} alkyl, alkoxyalkyl, arylalkyl or aryl, R^{10} is C_{1-17} alkyl, arylalkyl or aryl, R^{11} is hydrogen or C_{1-3} alkyl and said aryl and arylalkyl groups optionally can be substituted with one or more alkyl, alkoxy, amino, nitrile, sulphonamido groups or one or more halogen atoms.

13. A compound according to any of claims 1-12, wherein R^2 is 2-thienyl, 2-selenienyl, 2-furyl, 2-thiazolyl or 2-(1-methyl)-pyrrolyl or methoxyphenyl.

14. A compound of the formula I according to any of claims 1-13 for use in therapy.

15. A pharmaceutical composition comprising as an active ingredient a compound of the formula I according to any of claims 1-13 and a pharmaceutically acceptable carrier, including liposomes.

16. A method for therapeutic and/or prophylactic treatment of virus infections in an animal or human host in need of treatment, comprising administering an effective amount of a compound of the formula I as defined in any of claims 1-13.

17. A method according to claim 16 for treatment of infections caused by viruses requiring reverse transcriptase for replication, including human immuno deficiency virus and hepatitis B virus.

18. A method for treatment of aids comprising administering an effective amount of a compound of the formulaI as defined in any of claims 1-13.

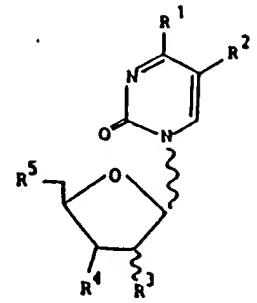
19. A method according to claim 16 for treatment of infections caused by herpes viruses.

20. Use of a compound of the formula I according to any of claims 1-13 for the manufacture of a medicament for therapeutic and/or prophylactic treatment of the acquired immuno deficiency syndrome and infections caused by viruses requiring reverse transcriptase for replication.

21. Use according to claim 20 for the treatment of infections caused by HIV-viruses.

C L A I M S

1. A compound of the formula

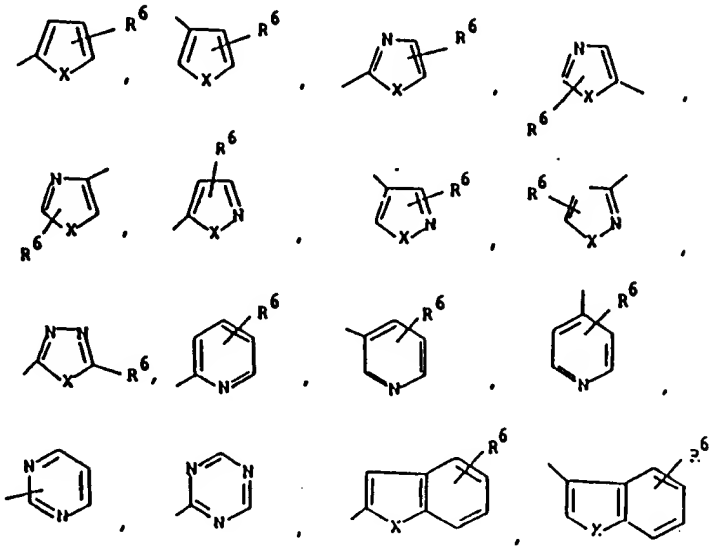


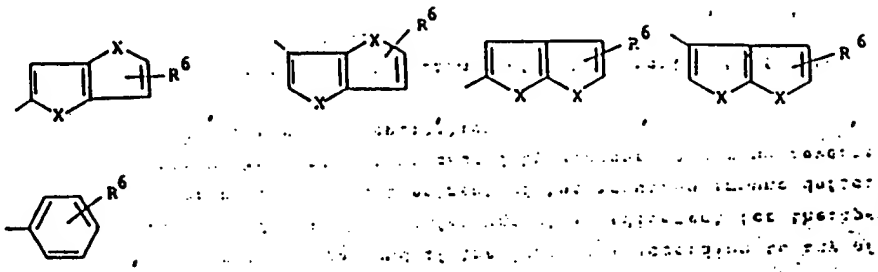
I

wherein the radicals R^1, R^2, R^3, R^4 and R^5 are defined as follows:

R^1: OH, NH_2;

R^2:





wherein X is O, S, N-R^7, Se;

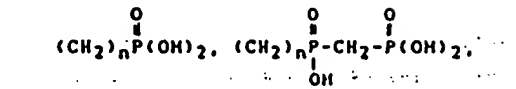
R^6 is H, straight or branched C_{1-10} alkyl, F, Cl, Br, I, X-R^7, -CH=CH-R^7, -C≡C-R^7, CO_2R^7, CH_2X-R^7;

R^7 is H, straight or branched C_{1-5} alkyl, phenyl;

R^3: H, OH, F, OCH_3;

R^4: H, F, OH or an ether or ester residue thereof, OCH_3, CN, C≡CH, N_3;

R^5: OH or an ether or ester residue thereof;



wherein n is 0 or 1 and H is hydrogen or a pharmaceutically acceptable counterion such as sodium, potassium, ammonium or alkylammonium; and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 in the form of an alpha anomer.

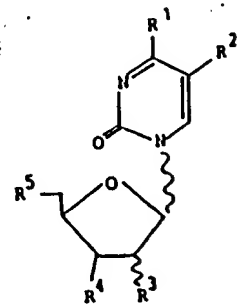
3. A compound according to claim 1 in the form of a beta anomer.

4. A compound according to claim 2 or 3, wherein the carbohydrate moiety has the arabinofuranosyl configuration.

5. A compound according to claim 2 or 3, wherein the carbohydrate moiety has the ribofuranosyl configuration.

22. Use according to claim 20 for the treatment of infections caused by hepatitis B virus.

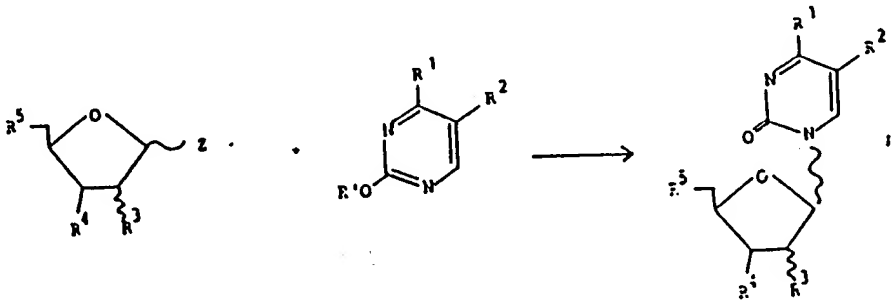
23. A process for preparation of a compound of the formula



I

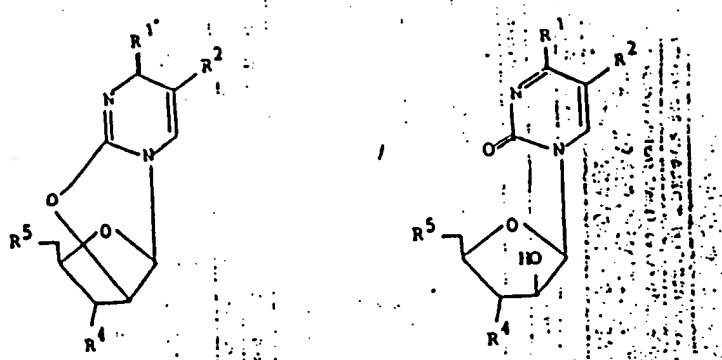
wherein R^1, R^2, R^3, R^4 and R^5 are as defined in claim 1, by

A. condensing a glycoside as comprised in formula I to the N-1 position of a pyrimidine derivative



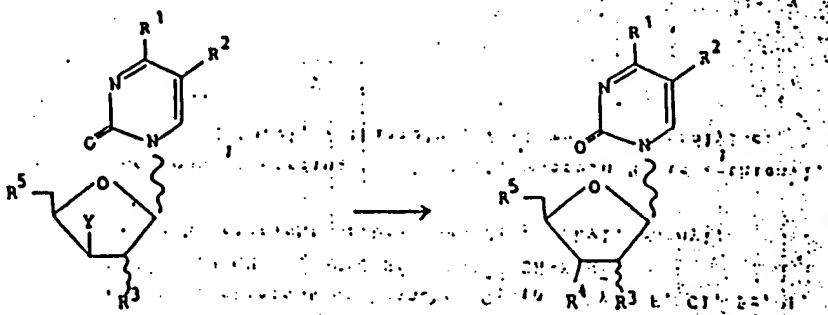
wherein Z is Cl, Br, I, acyloxy or alkoxy

B. hydrolyzing a 2,2'-anhydro nucleoside analogue to the corresponding β-anomer of the arabinosyl-pyrimidine nucleoside analogue



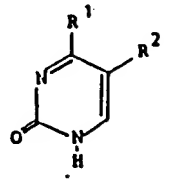
wherein $R^{1'}$ is O or NH;

C. substituting a derivatized hydroxyl group Y in the 3'-position of the glycon moiety by a fluoro, OCH_3, N_3, CN or CsCH substituent



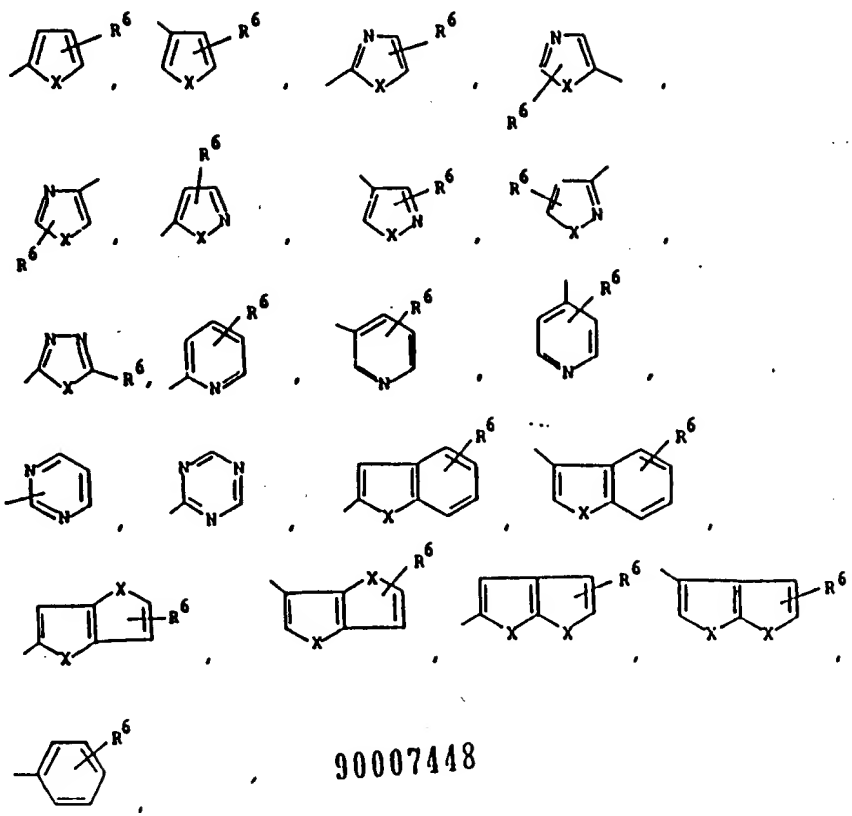
in which processes R^1-R^5 and n are as defined in claim 1 and optionally may be protected by suitable protecting groups.

24. A compound of the formula



I'

wherein the radicals R^1 and R^2 are defined as follows:
R^1: OH, NH_2;
R^2:



wherein X is O, S, N-R^7, Se;
R^6 is H, straight or branched C_{1-10} alkyl, F, Cl, Br, I, X-R^7, -CH=CH-R^7, -C≡C-R^7, CO_2R^7, CH_2X-R^7;
R^7 is H, straight or branched C_{1-5} alkyl, phenyl;

25. A compound according to claim 24, wherein R^2 is 2-thienyl, 2-selenienyl, 2-furyl, 2-thiazolyl, 2-(1-methyl)pyrrolyl or methoxyphenyl.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE89/00322

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)

According to International Patent Classification (IPC) or to both National Classification and IPC 4

C 07 H 19/06, 19/10, 19/24; A 61 K 31/70; C 07 D 239/47, 239/54, 401/04, 403/04, 405/04, 409/04, 421/04

II. FIELDS SEARCHED

Minimum Documentation Searched

Classification System	Classification Symbols
IPC 4	C 07 H

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	Anales de la real Academia de farmacia, Vol. 50 (1984):1, pages 57-65, Mohamed E. Hassan: "Photochemical synthesis of C-5 heteroaryl pyrimidine nucleosides".	1-15, 20-22
X	Tetrahedron Letters, Vol. 25, No. 2, pages 201-202, 1984, P. Vincent et al: "Synthese de Nucleosides substitues en C-5 par un carbocycle ou un heterocycle par couplages d'organozinciques avec L'IODO-5 O-bis(trimethylsilyl)-3',5' desoxy-2' uridine catalyses par des complexes organo-palladies".	1-15, 23
X	Chemical Abstracts, vol. 104, No. 23, 9 June 1986, (Columbus, Ohio, US), Hassan Mohamed E. "Photochemical synthesis of C(5)-alkyl and -hetercaryl-substituted pyrimidine nucleotides", see page 790, abstract 207587h, & Collect. Czech. Chem. Commun. 1985, 50(10), 2319-27 (Eng).	1,3,5,10,12,13

.../...

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1989-09-05	1989 -09- 13
International Searching Authority: Swedish Patent Office	Signature of Authorized Officer: Gunilla Claesson Gunilla Claesson

Form PCT/ISA/210 (second sheet) (January 1985)

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category*	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	Chemical Abstracts, vol. 98, no. 24, 13 June 1983, (Columbus, Ohio, US), Balzarini J. et al: "Structure-function relationship of the antitumor cell activity of pyrimidine and pyridine derivatives", see page 17 abstract 209571e, & Proc. Int. Round Table Nucleosides, Nucleotides Their Biol. Appl. 4th 1981 (Pub. 1982), 275-91.	1-15, 20-22
X	Tetrahedron Letters, vol. 21, 1980, pages 2813-2816, Isao Saito et al: "A simple synthesis of fluorescent uridines by photochemical method[1]".	1,3,5,6
X	Tetrahedron Letters, vol. 25, no. 23, 1984, pages 2431-2434, George Chang et al: "Palladium(0) Catalyzed Coupling Reactions in the Synthesis of 5-Arylpyrimidine Nucleosides".	1,3,5,6,13
X	J. Med. Chem. 1988, vol. 31, pages 1141-1147, George Chang et al: "Linear Free Energy Relationship Studies of Enzyme Active Site Bindning: Thymidylate Synthase".	1-15, 20, 23
X	Chemical Abstracts, vol. 98, no. 7, 14 February 1983, (Columbus, Ohio, US), Budesinsky Zdenek et al: "Some 1-β-D-ribofuranosyl-5-phenylcytosines and -5-(2-chlorophenyl)-2-thiocytosine", page 427, abstract 4734p, & Collect. Czech. Chem. Commun. 1982, 47(8), 2145-9 (Eng).	1-6, 23
X	US, A, 4 182 859 (SIEGFRIED ERHAROT) 8 January 1980 & DE, 2721466 JP, 53144586	1-15, 20-23
X	US, A, 4 211 773 (CARLOS LOPEZ ET AL.) 8 July 1980 & EP, 0010205 JP, 55049395 CA, 1131626 AU, 533135	1-15, 20-23
X	US, A, 4 666 892 (JACK J. FOX ET AL.) 19 May 1987 JP, 60252418 AU, 575918	1-15, 20-22
P,X	WO, A1, 8804662 (ASTRA LÄKEMEDEL AB) 30 June 1988 EP, 0294443	1-15, 20-22

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X	US, A, 4 211 773 (CARLOS LOPEZ ET AL.) 8 July 1980 & EP, 0010205 JP, 55049395 CA, 1131626 AU, 533135	1-15, 20-23
X	US, A, 4 666 892 (JACK J. FOX ET AL.) 19 May 1987 JP, 60252418 AU, 575918	1-15, 20-22
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